Hum. Reprod. Advance Access published December 9, 2004
doi:10.1093/humrep/deh664

Pregnancy outcome after IVF and ICSI in unexplained, endometriosis-associated and tubal factor infertility

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BACKGROUND: This study was undertaken in order to compare pregnancy outcome after IVF and ICSI in unexplained and endometriosis-associated infertility using tubal factor infertility as controls. METHODS: This was a retrospective cohort study of early IVF/ICSI pregnancies verified by serum hCG measurement, comparing the subsequent outcome in unexplained (n = 274) and minimal endometriosis-associated (n = 212) with tubal factor (n = 540) infertility as controls. From January 1990 to December 2002, 1026 conception cycles after treatment with IVF or ICSI complied with the inclusion criteria. RESULTS: Live birth rate, twin birth rate after transfer of two embryos and abortion rate prior to 6 weeks of gestation were superior for the unexplained (78.8, 23.5 and 11.7%) compared to endometriosis-associated (66.0, 15.0 and 19.3%) and tubal factor (66.7, 18.1 and 18.0%) infertility groups ($P < 0.05$). Compared to the endometriosis-associated, the unexplained infertility group attained a higher pregnancy rate after the first treatment cycle ($P < 0.05$). CONCLUSIONS: The overall better outcome for the unexplained infertility group with respect to live birth rate, twin birth rate and early abortion rate compared to the minimal peritoneal endometriosis-associated and tubal factor infertility groups might be a guide to select diagnostic groups for single embryo transfer and be useful in patient counselling.

Key words: endometriosis/IVF/pregnancy outcome/unexplained infertility

Introduction

First trimester abortions are common both in spontaneous pregnancies and pregnancies after treatment with assisted reproductive techniques. Approximately one-third of all pregnancies result in spontaneous abortions (Wilcox *et al.*, 1988). This estimate could be reduced by nearly two-thirds in clinically verified pregnancies (Zinaman *et al.*, 1996). Genetic abnormalities, uterine anatomic defects (congenital and acquired), environmental factors such as smoking and drugs, antiphospholipid antibodies, increased maternal age and obesity are factors believed to contribute to spontaneous abortions both in natural and assisted reproduction conceptions (Andersen *et al.*, 2000; Cramer and Wise, 2000; Garcia-Enguidanos *et al.*, 2002; Fedorcsák *et al.*, 2004). Preimplantation diagnostic techniques can reduce transfer of aneuploid embryos but demand large resources and pose ethical dilemmas. Several studies, however, report similar or increased abortion rates after IVF and ICSI compared to the general population (FIVNAT, 1995; Schieve *et al.*, 2003; Wang *et al.*, 2004). Because of generally earlier and consequent hCG sampling in assisted reproduction pregnancies compared to spontaneous pregnancies, the incidence of the latter could be underestimated, as women might not recognize very early pregnancy loss occurring as such but rather as delayed menstrual discharge.

Differences in pregnancy outcome after assisted reproduction treatment in unexplained and minimal peritoneal endometriosis-associated infertility might reflect some of the different factors involved in patients' difficulties to conceive. Indeed, previous studies have shown that embryo quality and implantation rate are reduced in infertile women with endometriosis undergoing IVF, whereas endometrial receptivity seems to be unaffected (Simón *et al.*, 1994; Garcia-Velasco *et al.*, 2001; Garrido *et al.*, 2002). In a study from our own group, comparing the outcome in unexplained infertility with minimal peritoneal endometriosis-associated infertility (ASRM stage I; American Society for Reproductive Medicine, 1997), similar cleavage and implantation rates were found (Tanbo *et al.*, 1995a). However, in a meta-analysis, endometriosis-associated infertility was found to have a negative impact on pregnancy rate, fertilization rate and implantation rate compared with tubal factor infertility (Barnhart *et al.*, 2002).

Controlled ovarian stimulation (COS), whether in artificial insemination by husband (AIH), IVF or ICSI, seems to overcome important factors of unexplained infertility. The relative abundance of oocytes after COS seems to increase the possibility of fertilization and development of more viable embryos both *in vivo* and *in vitro* despite possible oocyte or sperm dysfunction (Hull *et al.*, 1998). Because fertilization

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rates were found to increase when donor sperm were used as an alternative to homologous insemination in IVF treatment of unexplained infertile couples, a possible male factor is suspected (Hull *et al.*, 1998). The unfavourable pregnancy outcome in endometriosis-associated compared to the unexplained infertility group might support the theory of an ovarian component in the former (Cahill and Hull, 2000). Furthermore, the endometriosis-associated inflammatory reaction in the peritoneal cavity with increased levels and activity of peritoneal macrophages and their secretory products, such as cytokines, is believed to contribute to the subfertility (Wu and Ho, 2003). The presumed gamete and embryo toxicity of the peritoneal fluid in women with endometriosis might also explain the reduced pregnancy rate in treatment with AIH in endometriosis-associated compared to unexplained infertility (Omland *et al.*, 1998).

In endometriosis-associated infertility the findings of impaired follicular growth and hormonal levels suggest a possible pituitary–ovarian endocrine dysfunction in addition to granulosa cell dysfunction that might have a negative influence both on oocyte function and fertilization ability compared to unexplained infertility (Harlow *et al.*, 1996; Cahill and Hull, 2000).

With the increasing knowledge of higher abortion rates and complications in multiple pregnancies, couples in need of assisted reproduction might experience the dilemma of choosing single embryo transfer (SET) with possibly reduced success rate over multiple embryo transfer. To individualize patient counselling, the probable success rate of each couple should be assessed. Accumulated data on assisted reproduction outcome might be compared between different diagnostic infertility groups for better guidance. The present cohort study was undertaken in order to assess and compare possible differences in pregnancy outcome after IVF and ICSI in unexplained and endometriosis-associated infertility using tubal factor infertility as controls.

Materials and methods

A cohort of 1026 consecutive pregnancies in couples with unexplained ($n = 248$), minimal endometriosis-associated ($n = 184$) (ASRM stage I) and tubal factor ($n = 479$) infertility was collected from all IVF and ICSI cycles performed in our fertility unit between January 1990 and December 2002.

Tubal factor infertility was diagnosed by laparoscopy or, in some cases, by laparotomy and registered as one entity (tubal factor) in our database, regardless of type, for example hydrosalpinx, medial or lateral occlusion. Laparoscopy was also performed in unexplained and endometriosis-associated infertility groups. In unexplained infertility, laparoscopy was normal, in endometriosis-associated infertility it indicated minimal peritoneal endometriosis lesions (ASRM stage 1). The endometriosis-associated infertility group consisted of untreated patients and patients who had received medical or surgical treatment for endometriosis. Inclusion criteria for the women were: maximum age 37 years, minimum 2 years of infertility, regular menstrual cycle (interval 25–35 days) with luteal phase progesterone >15 nmol/l and normal concentrations of prolactin, free thyroxin and thyroid-stimulating hormone (TSH). Patients with polycystic ovaries were excluded. Within 1 year prior to treatment, at least one semen analysis in each included couple should be normal as defined by the latest World Health Organization (WHO) laboratory manual for semen analysis at the actual time (WHO, 1988, 1992, 1999). Only cycles with standardized ovarian stimulation protocol for IVF and ICSI were included.

Pituitary down-regulation with a GnRH agonist (buserelin acetate: Suprefact® or Suprecur®, Hoechst, Germany; nafarelin acetate: Synarela®, Pharmacia, Norway) was used in all patients as intranasal application from the mid-luteal phase of the previous menstrual cycle, followed by daily injections of hMG (Pergonal®, Serono, Switzerland; Humegon®, Organon, The Netherlands), urofollitropin (Fertinorm®, Fertinorm-HP®, Serono) or human recombinant FSH from 1996 and onwards (Gonal F®, Serono; Puregon®, Organon). Oocyte retrieval was performed 34–36 h after administration of 10 000 IU hCG (Profasi®, Serono; Pregnyl®, Organon), using a standard ultrasound-guided transvaginal approach. Progesterone [25 mg/day in oil i.m. or 600 mg intravaginal Progestan® capsules (Organon) or 90 mg intravaginal gel Crinone® (Maropack AG, Switzerland)] was administered for luteal phase support for 2 weeks starting the day after oocyte retrieval. Collected oocytes were fertilized *in vitro* by IVF or ICSI (Åbyholm *et al.*, 1990; Tanbo *et al.*, 1998). ICSI was introduced in 1995 and in this cohort only offered to couples who previously had experienced at least one IVF cycle with no or maximum of 20% fertilization rate despite normal semen parameters according to WHO criteria. Fertilization rate was defined as the fraction of zygotes with two pronuclei present the day after retrieval (day 1). However, prior to August 1993, embryos were evaluated for fertilization 2 days after retrieval (day 2) for cleavage stage and number of blastomeres. Their fertilization was thus assessed as the fraction of cleaved embryos on day 2 and is given as cleavage rate. During the study period the number of embryos transferred was gradually reduced from four to two. Only cycles with transfer of fresh embryos were included. Pregnancy was verified by plasma β-hCG >20 IU/l 14 days after oocyte retrieval (Bjercke *et al.*, 1999). The implantation rate was calculated as the fraction of number of embryos implanted per transferred embryos. Gestational age was calculated by adding 2 weeks to the oocyte retrieval date. Spontaneous abortions before the sixth week were defined as transiently elevated plasma β-hCG with a concomitant delayed menstrual period. All other pregnancies were confirmed by vaginal ultrasound visualization of viable or non-viable fetus 5–6 weeks after transfer. The first trimester vanishing twin diagnosis was made when only one of previously two gestational sacs was observed during a later ultrasound investigation.

Deliveries prior to 161 days (23 weeks) of gestation were classified as abortions. Preterm deliveries were defined as births between 161 and 259 days (37 weeks) of gestation, term deliveries as births between 259 and 294 days (42 weeks) of gestation. Stillbirth was used for infants stillborn after 161 days of gestation.

Statistics

SPSS version 12 (SPSS Inc., USA) was used for data analysis. Continuous data with normal distribution are given as mean ± SD, otherwise as median (range) values. One-way analysis of variance (ANOVA) with Bonferroni adjustment was used to compare normally distributed continuous variables between the three groups. Non-parametric data were examined with the Kruskal–Wallis test. Comparison of categorical variables was performed with the χ^2-test or Fisher's exact test in case of any infrequent response. To further model spontaneous abortions, gestational length and birthweight logistic regression was used with age, diagnostic group and body mass index (BMI) as independent variables. $P < 0.05$ was considered statistically significant.

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Table I. Patient characteristics

Infertility group	Unexplained	Endometriosis-associated	Tubal factor
Couples (*n*)	248	184	479
Conception cycles (*n*)	274	212	540
Age, years (mean ± SD)	32.6 ± 3.4	32.3 ± 3.4	32.7 ± 3.5
Body mass index, kg/m^2 (mean ± SD)	23.7 ± 4.0[a]	22.3 ± 2.9	23.7 ± 4.1[a]
Years of infertility (mean ± SD)	5.4 ± 2.4	5.0 ± 2.0	5.6 ± 3.0

[a]$P < 0.05$ compared to endometriosis-associated infertility.

Results

Patient characteristics are shown in Table I. There were no differences in age or duration of infertility among the three groups. In the endometriosis-associated infertility group, the mean BMI was lower ($P < 0.05$); only 12.9% had a BMI above normal (>25 kg/m^2) compared to 28.7% in unexplained and 27.0% in the tubal factor infertility groups ($P < 0.05$).

Results of ovarian stimulation, oocyte retrieval and fertilization are shown in Table II. More couples with unexplained infertility were treated with ICSI ($P < 0.05$). There were no differences in other outcome parameters. For all groups the semen characteristics on the day of oocyte retrieval were within the normal range. However, mean total motility and rapid progressive motility were lower in the unexplained compared to endometriosis-associated and tubal factor infertility groups ($P < 0.05$) (Table II).

The frequencies of one, two or three conception cycles per couple were as follows: unexplained infertility 90.7, 8.9, 0.4%; endometriosis 87.1, 12.4, 0.5%; tubal infertility 88.8, 10.1, 1.1%. Prior to extracting the cohort of 1026 consecutive pregnancies, the number of conceptions in the first treatment cycle was calculated: 58.8% in the unexplained, 48.6% in the endometriosis-associated and 54.8% in the tubal factor infertility groups conceived ($P < 0.05$ when comparing unexplained with endometriosis-associated infertility).

Table II. Treatment cycle characterisitcs

Infertility group	Unexplained	Endometriosis	Tubal factor
Total no. of cycles	274	212	540
ICSI cycles (*n*, %)	32 (11.7)[a,b]	14 (6.6)	24 (4.4)
hMG/FSH total dose (IU) (mean ± SD)	1962 ± 784	1873 ± 719	1999 ± 723
Days of stimulation (mean ± SD)	10.7 ± 1.9	10.6 ± 1.8	11.0 ± 2.3
No. of oocytes (*n*, mean ± SD)	10.2 ± 5.7	9.4 ± 4.9	10.0 ± 5.6
Sperm characteristics			
Concentration (×10^6/ml)	140 ± 88	151 ± 91	150 ± 89
Motility (%)	54 ± 21[a,b]	57 ± 20	61 ± 20
Rapid progressive motility (%)	27 ± 14[a,b]	31 ± 15	33 ± 15
Normal morphology (%)	38.0 ± 16.0	40.6 ± 12.3	42.2 ± 14.3
Fertilization rate (%, mean ± SD)	65.5 ± 22.8	68.7 ± 22.8	68.7 ± 20.3
Cleavage rate (%, mean ± SD)	75.6 ± 23.5[c]	61.3 ± 27.0[d]	80.3 ± 21.5[e]
Embryos transferred (median, range)	2 (1–3)	2 (1–4)	2 (1–4)

[a]$P < 0.05$ compared to endometriosis-associated infertility.
[b]$P < 0.05$ compared to tubal factor infertility.
[c]$n = 26$;
[d]$n = 18$;
[e]$n = 11$.

Table III. Pregnancy outcome

Infertility group	Unexplained ($n = 274$)	Endometriosis ($n = 212$)	Tubal factor ($n = 540$)
Gestational sacs (median, range)	1.00 (0–3)	1.00 (0–3)	1.00 (0–2)
Implantation rate (mean ± SD)	61.0 ± 28.3	58.1 ± 27.2	59.8 ± 24.8
Live births (*n*, %)	216 (78.8)[a,b]	140 (66.0)	360 (66.7)
Singletons (*n*, % of live births)	154 (71.0)	105 (75.0)	269 (74.7)
Twins (*n*, % of live births)	61 (28.1)	33 (23.6)	91 (25.3)
Triplets (*n*, % of live births)	2 (0.9)	2 (1.4)	0
Abortions (*n*, %)			
<6 weeks	32 (11.7)[a,b]	41 (19.3)	97 (18.0)
6–12 weeks	20 (7.3)	24 (11.3)	61 (11.3)
>12 weeks	4 (1.5)	4 (1.9)	5 (0.9)
Extrauterine pregnancies (*n*, %)	2 (0.7)[b]	2 (0.9)	15 (2.8)
Stillbirths (*n*, %)	0	1 (0.5)	2 (0.4)

[a]$P < 0.05$ compared to endometriosis-associated infertility.
[b]$P < 0.05$ compared to tubal factor infertility.

Pregnancy outcome is summarized in Table III. No differences in the implantation rate or the numbers of gestational sacs were observed. The unexplained infertility group had a higher live birth rate compared to both the endometriosis-associated and tubal infertility groups ($P < 0.05$). There was no difference in the frequency of singleton or twin births between the groups. However, when comparing pregnancy outcome after transfer of two embryos exclusively, the unexplained infertility group had a higher incidence of twin births (23.5%) compared to the endometriosis-associated (15.0%) and tubal factor (18.1%) infertility groups ($P < 0.05$ when comparing unexplained and endometriosis-associated infertility).

The spontaneous abortion rate prior to the sixth gestational week was lower in the unexplained infertility group compared to the two other groups ($P < 0.05$), while the abortion rates between the sixth and 12th week and after the 12th gestational week were similar for all three groups. When the total frequencies of first trimester fetal demise are compared, a highly significantly lower abortion rate is observed in the unexplained infertility group compared with endometriosis and tubal infertility: 19.0, 30.7 and 29.3% respectively ($P < 0.003$). When excluding the women with BMI >25 kg/m^2, this difference persisted with abortion rates of 15.9, 28.2 and 27.2% for the unexplained, endometriosis-associated and tubal factor infertility groups respectively ($P < 0.009$). For the women with BMI >25 kg/m^2 we found no such difference among the groups (23.5, 25.0 and 37.1% respectively, $P = 0.11$).

When adjusted for age and BMI, the probability of first trimester miscarriage remained higher both for the peritoneal

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endometriosis infertility group [odds ratio (OR) = 1.96, $P = 0.004$, 95% confidence interval (CI) = 1.25–3.09] and the tubal factor infertility group (OR = 1.88, $P = 0.001$, CI = 1.29–2.73) compared to the unexplained infertility group. For the total cohort, the probability of first trimester miscarriage was higher when BMI $>25\,kg/m^2$ compared to BMI $<25\,kg/m^2$ (OR = 1.6, $P = 0.008$, CI = 1.14–2.30).

In the tubal factor infertility group the rate of extrauterine pregnancies was increased compared to the unexplained infertility group. Two tubal factor pregnancies turned out to be heterotopic; both women delivered a singleton after the tubal pregnancy was removed in the first trimester.

In the twin pregnancies, where two gestational sacs were observed 4–6 weeks after embryo transfer, first trimester vanishing twin was observed in one case in the unexplained, two cases in the endometriosis-associated and 10 cases in the tubal factor infertility groups.

Gestational age and birthweights are summarized in Table IV. Of the babies born, a total of 90.8% of the offspring was delivered at term; 95.3% of the singletons and 79.9% of the multiple pregnancies. No differences between the infertility groups were observed. After adjusting for age and BMI, the probability of a singleton delivery prior to 32 weeks (224 days) of gestation was not different in the three groups. The probability of preterm delivery (<37 weeks/259 days) was similar for the unexplained and endometriosis-associated infertility group (OR = 1.03, $P = 0.36$, CI = 0.9–1.28). However, compared to the unexplained infertility group, the tubal factor group had a higher probability of preterm deliveries (OR = 2.41, $P = 0.006$, CI = 1.29–4.50). The mean gestational age at delivery was similar both for singletons and for twins in unexplained, endometriosis-associated and tubal factor infertility (Table IV).

There were no differences in mean birthweights in the unexplained, endometriosis-associated or tubal factor infertility groups for singletons, or for twins. In the three groups the probability of obtaining a singleton with birthweight <1500 g was similar. However, when comparing the singleton birthweight <2500 g in the three groups, the probability was higher for the tubal factor infertility group compared to the unexplained infertility group (OR = 4.4, $P = 0.018$, CI = 1.3–14.9) and no difference was found between the latter and the endometriosis-associated infertility group (OR = 2.6, $P = 0.178$, CI = 0.6–11.70).

Table IV. Gestational age and birthweight

Infertility group	Unexplained ($n = 274$)	Endometriosis ($n = 212$)	Tubal factor ($n = 540$)
Singletons (days, mean ± SD)	275 ± 19	275 ± 13	272 ± 19
Singletons (g, mean ± SD)	3462 ± 574	3452 ± 601	3396 ± 698
Singletons birthweight (*n*, %)			
> 2500 g	169 (86.2)	100 (87.7)	282 (83.3)
< 2500 to > 1500 g	20 (10.2)	13 (11.4)	46 (13.6)
< 1500 g	7 (1.5)	1 (0.9)	11 (3.2)
Twins (days, mean ± SD)	255 ± 19	255 ± 18	254 ± 22
Twins (g, mean ± SD)	2525 ± 594	2641 ± 539	2571 ± 657

The frequencies of spontaneous, operative vaginal and Caesarean deliveries were similar between the three groups with 61.9, 9.7 and 28.4% in unexplained, 63.2, 14.9 and 21.8% in endometriosis-associated and 62.8, 10.5 and 26.7% in the tubal factor infertility groups.

Three stillbirths occurred; all were singletons diagnosed by ultrasound as intrauterine fetal deaths, one in the endometriosis-associated (27th gestational week) and two in the tubal factor group (gestational weeks 24 and 29).

In the unexplained infertility group, one set of triplets was stillborn and one singleton died after birth in the 22nd gestational week.

In another two twin pregnancies, intrauterine death of one fetus was observed in the 19th and 22nd gestational week in the endometriosis-associated infertility group. Both women gave birth to healthy singletons at term.

In the singleton deliveries, 15 major malformations were reported, seven in the unexplained, one in the endometriosis-associated and seven in the tubal factor infertility groups. The malformations consisted of two trisomies 21, one hydrocephalus, three heart conditions (patent ductus arteriosus, open foramen ovale and aortopulmonary malformation) and seven orthopaedic deformities (one torticollis, three hip dysplasia, three foot deformities and one cystic finger tumour), one osteogenesis imperfecta and one serious syndrome (hyperthyroidism, antimongoloid eye direction, broadness at the base of the nose and ears situated lower than normal). In the twin deliveries, one heart condition (patent ductus arteriosus), a couple of premature twins with serious heart condition (large patent ductus arterious) who died after surgery, one multicystic kidney dysplasia and four foot deformities were found. In one set of triplets, two siblings were reported with inguinal hernias and testicular retention.

Discussion

This study shows lower first trimester abortion rate, higher first treatment cycle pregnancy rate, higher live birth rate and more twin births after transfer of two embryos in the unexplained infertility group. This might indicate more viable embryos and perhaps a more agreeable environment to support a pregnancy after IVF and ICSI in the unexplained compared to the endometriosis-associated and tubal factor infertility groups. Although not significantly different, the higher number of vanishing twins in the endometriosis-associated and tubal factor compared to the unexplained infertility groups also agrees with the tendency of more successful pregnancy outcome in the latter.

As peritoneal endometriosis after a second laparoscopy can be diagnosed in women with previous negative laparoscopic findings, it might not be surprising that hormonal investigations in unexplained and peritoneal endometriosis-associated infertility often yield similar results (Cahill *et al.*, 1995; Akande *et al.*, 2000; Omland *et al.*, 2001). Hormonal factors could be influenced and apparently improved with COS for unexplained and peritoneal endometriosis-associated infertility. However, with the presence of peritoneal endometriosis a hostile environment of macrophages, cytokines

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and vasoactive substances is observed and these factors are not easily overcome by COS combined with IVF and ICSI (Pellicer *et al.*, 1998). Biochemical abnormalities have been observed in histologically normal eutopic endometrium of endometriosis-associated infertility (Giudice, 2003). These factors might also be a contribution to the adverse pregnancy outcome of the endometriosis-associated compared to the unexplained infertility groups in the present study.

We were unable to show any significant difference in fertilization and cleavage rates between the groups in this pregnant cohort. However, the higher number of ICSI cycles and the lower sperm motility in the unexplained infertility group could indicate a higher incidence of fertilization defects in this group since ICSI was applied only after previous IVF failure. The semen parameters were comparable for all groups in the ICSI cycles and within normal range (data not shown). This supports previous findings suggesting a possible male contribution in some patients with unexplained infertility (Hull *et al.*, 1998).

The inferior outcome of the tubal factor compared to the unexplained infertility group of this study was surprising, as IVF is considered to be an ideal treatment option for this mechanical failure to conceive. Our data were, however, incomplete as to registration of smokers and the presence of clinically verified hydrosalpinx. A bias in these factors could influence the results. The higher number of infants with birthweight <2500 g in the tubal factor group might be a consequence of the higher incidence of preterm births compared to the unexplained and endometriosis-associated infertility groups.

Data were insufficient to compare outcome in treated and non-treated endometriosis. However, Marcoux *et al.* (1997) could not show any differences in early pregnancy loss between two endometriosis-associated infertility groups with and without laparoscopic ablation of endometriosis.

We could not compare between elective and emergency Caesarean sections and induced or spontaneous labour due to insufficient data. In a previous study from our group, both higher elective and emergency Caesarean section rate of 14.6 and 13.7% respectively in IVF pregnancies compared to 8.6 and 10.8% in spontaneous pregnancy control group ($P < 0.05$) were found (Tanbo *et al.*, 1995b). The higher incidence of Caesarean section in this study could partly be caused by the overall higher incidence of elective Caesarean section in general since 1995. Our data did not allow us to correlate birthweight and gestational length to possible emergency preterm deliveries and accordingly possible differences between the groups.

Optimal treatment of assisted reproduction is considered to be singleton pregnancies because they have better outcome than multiple pregnancies (ESHRE Capri Workshop Group, 2003). Multiple pregnancies are more frequent after assisted reproduction treatment than in spontaneous cycles. The consequences of multiple pregnancies for the children, the mother, the family and the society are often emphasized and it has been recommended to perform SET, and to report multiple pregnancies as complications and not as success (Shenfield *et al.*, 2003). A recent review on perinatal outcome after assisted reproduction treatment concluded that singleton pregnancies have worse perinatal outcome than spontaneous pregnanies (Helmerhorst *et al.*, 2004). The data were insufficient to correct for possible adverse effects of vanishing twins, a consequence of multiple embryo transfer and a rare observation in natural conceptions. This bias could be corrected by comparing natural conceptions and assisted SET conceptions. However, as assisted reproduction treatment in most countries is expensive, instituting SET with possible reduction in pregnancy rates in order to avoid multiple pregnancies may be difficult to accept for the couple.

In conclusion, compared to the minimal endometriosis-associated and tubal factor infertility groups, the unexplained infertility group in this pregnant cohort was the most successful one after IVF and ICSI. The unexplained infertility group had higher first treatment cycle pregnancy rate, lower first trimester abortion rate and consequently higher live birth rate in addition to more twin births after transfer of two embryos exclusively. These results might be a guide for selecting groups suitable for SET and useful in counselling patients with regard to more realistic expectations prior to treatment.

Acknowledgements

Geir Aamodt, PhD, Section of Biostatistics, National Hospital, Oslo, Norway kindly performed statistical analyses.

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Submitted on August 31, 2004; accepted on November 19, 2004

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